Preview: Image-Guided Therapy using Maghemite-MOF Nanovectors

Isabel Abánades Lázaro and Ross S Forgan*

WestCHEM School of Chemistry, University of Glasgow, Joseph Black Building, University Avenue, Glasgow, G12 8QQ, UK

E-mail: Ross.Forgan@glasgow.ac.uk

Advances in nanotechnology offer the possibility of tailored delivery of therapeutics with real-time imaging of disease. In this issue of *Chem*, Steunou *et al.* amalgamate the powerful magnetic resonance imaging properties of ultra-small paramagnetic iron oxides with the excellent drug delivery capabilities of metal-organic frameworks to produce theranostic nanoparticulate devices for cancer treatment and imaging.

Cancer is a price that the human race has had to pay as a consequence of our remarkable evolution. It is estimated that between one third and one half of the population of developed countries will be diagnosed with cancer at some point in their lives, and so advancing the treatment and diagnosis of cancer remain a priority for the scientific community. Most available therapeutics still have many side-effects as a consequence of the potency required to overcome the high resistance and invasion of cancer tissue, while some tumours have developed resistance to drugs such as doxorubicin. Attempts to overcome these and other problems associated with emerging therapeutics have led to the development of drug delivery systems (DDSs) to enhance bioavailibity, selectivity, and efficacy, while facilitating complementary imaging. In this context, nanotechnology offers the possibility of preparing Trojan horses, loaded with anti-cancer therapeutics, to be selectively internalised by damaged cells. Through engineering of their structure and constitution, effective diagnosis, treatment, and imaging may be achieved simultaneously by a single nanovector; so called theranostics. However, shortcomings such as poor drug loading, uncontrollable release of the drug, difficulty of crossing membrane barriers, immune system recognition, accumulation in the body, and cytotoxicity, among others, can hinder the anti-cancer potential of these devices.[1] In this issue of *Chem*, Steunou and co-workers combine the excellent drug delivery properties of metal-organic frameworks (MOFs) with novel magnetic resonance imaging (MRI) contrast agents – ultra-small superparamagnetic iron oxides (USPIOs) – to produce efficient theranostic devices.[2]

MOFs are composed of metal ions or clusters bridged by multidentate organic linkers into extended networks, and offer several advantages compared to other classes of DDSs. Their remarkably high porosities provide higher drug payloads, while the tuneable nature of the metal clusters and organic likers offers the possibility of creating specialised biocompatible materials with controlled drug release and engineered surfaces.[3] The authors selected MIL-100(Fe), a highly porous iron MOF linked by 1,3,5-benzenetricarboxylate ligands (Figure 1a) with validated *in vitro* and *in vivo* potential as an anti-cancer DDS, for study.[4] An advantage of using MOF-based drug delivery systems is that the metal cations, as well as acting as key structural components, can be exploited for medical imaging. Gadolinium chelate complexes have been widely used in MRI treatments, and it has been found that Gd^{3+} based MOFs can also act as efficient T_1 and T_2 MRI contrast agents. However, poor physiological

stability often results in toxicity, inducing nephrogenic systemic fibrosis, which is a complication derived from treatment with gadolinium based contrast agents.[5]

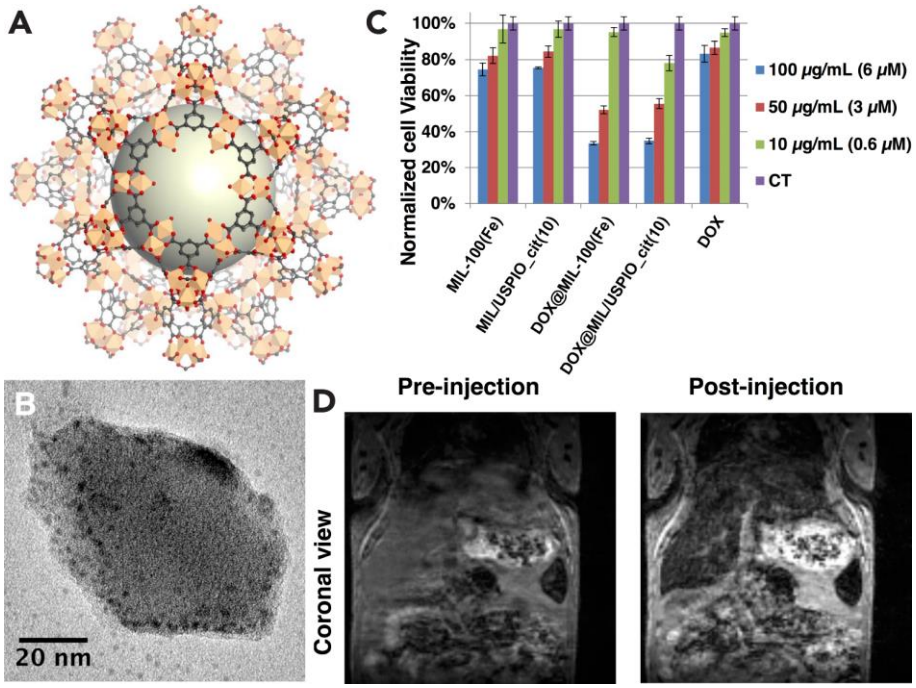

Figure 1. a) Portion of the solid-state structure of MIL-100(Fe). b) TEM image of MIL/USPIO-cit. c) Normalised PC3 cell viabilities when exposed to different doses of the loaded and unloaded MOF vectors. d) 3D T2*-weighted gradient echo images of the mouse abdomen before and after injection of the MOF-USPIO material.

Ultra-small superparamagnetic iron oxides (USPIOs) such as maghemite (Υ-Fe_2O_3) are a novel category of clinically used MRI contrast agents, as they have remarkable sensitivity in T_2* weighted images that leads to negative image enhancement, and can be used in doses low enough to avoid deleterious side effects.[6] Due to their small size, they have long plasma half-lives and, more importantly, they allow differentiation between normal-size metastatic and healthy lymphonodes. USPIOs have also been studied for other applications such as magnetically responsive drug delivery and magnetic targeting, among others. As magnetic nanoparticles release heat upon magnetisation, USPIOs can induce localised cancer cell death, without damaging healthy tissue, in so-called hyperthermia-based anticancer treatment.[7] Although other DDSs, such as mesoporous silica, have been investigated in combination with USPIOs for MRI applications, the resultant materials had low values of relaxivities and magnetic saturation, and they induced cytotoxicity, which has so far limited their applications.[8]

Only a few MOF-iron oxide composites have been reported for drug delivery, usually resulting in low magnetic saturation, which hinders their MRI application.[9,10] By combining the properties of MIL-100(Fe) and USPIOs, Steunou *et al.* report a doxorubicin-loaded MOF-iron oxide composite with applications in image-guided anti-cancer therapy, offering not only remarkably high magnetic saturation and relaxivity values, but also better anti-cancer efficiency than the free drug.

To prepare the composites (Figure 1b), the authors cleverly took advantage of the differing surface chemistries of the components. After synthesising MIL-100(Fe) MOF nanoparticles (130 ± 30 nm),

uncoated USPIOs NPs (7 ± 3 nm) and USPIOs covalently modified with citrate (USPIO-cit) separately in aqueous solvents, surface potentials were measured across a wide pH range. Combining aqueous solutions of the MOF and the USPIOs at a pH where the materials exhibit opposite surface charges ensures efficient coupling of the agents with fine control over MOF:USPIO ratios. This green chemistry approach might overcome some of the issues regarding the manufacturing of MOF DDSs. The authors proved that both species conserve their structural integrity after their association, and found evidence that MIL-100(Fe) and USPIOs-cit are coupled covalently through the carboxylic groups of the citrates present at the surfaces of USPIO-cit. More importantly, one of the biggest drawbacks of nanoparticulate DDSs – aggregation in simulated biological conditions – was proven to be negligible. Dynamic light scattering experiments in phosphate buffered saline spiked with bovine serum albumin (BSA) showed little aggregation after 72 hours, due to the formation of a BSA protein corona on the outer surfaces of the nanoparticles, which favours dispersion and maintains the cohesion of both counterparts.

Horcajada *et al.* previously investigated the application of various iron-carboxylate MOFs as MRI contrast agents, demonstrating *in vivo* that they behaved similarly to iron oxides, with high values of transverse relaxivity (r_2).[4] These MRI properties have been greatly improved upon association with USPIO–cit. The authors coupled ^{57}Fe Mossbauer spectrometry and vibrating sample magnetometry in order to characterise the composites' magnetic properties, which have been reported for the first time for this type of material. At 10% *w/w* loading of USPIO-cit, the MOF-USPIO composite has the highest value of transverse relaxivity reported for MOF-based vectors, and the values are similar to clinically approved contrast agents. These new materials possess excellent magnetic and relaxometric properties, with values of magnetic saturation consistent with USPIOs, and the composite can be considered a T_2-MRI agent with reproducible r_2 values, which can also act as a T_1 agent.

As only small amounts of USPIOs are needed to facilitate this efficient imaging performance, the MOFs retained their porosity after conjugation, allowing the authors to load the pores with the anti-cancer drug doxorubicin. Importantly, by slightly modifying previously reported loading protocols, the authors were able to enhance the drug payload from 9% *w/w* to 14% *w/w*, finding gradual, sustained cargo release profiles lasting up to 25 days. *In vitro* cytotoxicity studies (Figure 1c) showed that while empty MOFs and MOF-USPIO–cit composites did not have notable negative effects on the viability of prostate cancer cells (PC3 cell line), when loaded with doxorobucin their cytotoxicity was significantly higher than the free drug. Furthermore, the *in vivo* application of these materials as MRI contrast agents was clearly validated in mice. As a consequence of their high T2* effect, a homogeneous decrease of the liver and spleen signal was observed (Figure 1d), generating a 52% decrease of signal-to-noise ratio, and suggesting rapid internalisation of the MOF-USPIO composites.

The results obtained by Steunou and colleagues strongly suggest that these MOF-USPIO composites are members a new generation of theranostic devices, coupling therapeutic delivery and high-resolution vascular imaging contrast agents, which will open up routes to diverse further applications for composites of MOFs and nanomaterials. An obvious next step would be to assess the therapeutic efficiency of the materials *in vivo* with real-time imaging of the treatment. Surface modifications of the MOF-USPIOs composites with targeting units, for example molecules able to selectively bind to proteins overexpressed by cancer tissue, could enable selective anti-cancer treatment, while being able to simultaneously observe the tumour remission by MRI. The war against cancer will obviously continue, and indeed total victory may never be fully achieved, but development of novel agents such as these may help win some battles along the way.

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